

A Note from NIDA

This special neuroscience issue of NIDA NewsScan was created to coincide with the Frontiers in Addiction Research: NIDA Mini-Convention, a satellite meeting on November 12 at the Society for Neuroscience 40th Annual Meeting. This special issue, which summarizes recently published research from the National Institute on Drug Abuse, will be posted on the NIDA website on November 12 at <http://www.drugabuse.gov/newsroom/10/NS-11.html>. The NIDA conference agenda can be viewed at <https://www.seiservices.com/nida/frontiers2010/agenda.aspx>.

Research News

Novel local communication system in key brain reward area

The ventral tegmental area (VTA), a region of the midbrain associated with pleasure, reward and craving, plays a key role in drug abuse and addiction. The VTA contains several types of neurons, including those that release dopamine (DA), GABA, and glutamate. By studying both anatomical and electrophysiological properties of the VTA from male rats, NIDA researchers were able to learn more about the connectivity of VTA glutamatergic neurons and their projections. Researchers found that glutamatergic neurons in the VTA make local synapses (or connections) on both DA as well as non-DA neurons. In addition, results from the electrophysiology studies suggest that glutamatergic neurons inside the VTA may play a key role in controlling cell firing patterns of other VTA neurons. These findings expand the known modalities of local communication in the VTA and may also provide potential targets for the development of novel therapies.

Dobi A, Margolis EB, Wang HL, Harvey BK, Morales M. Glutamatergic and nonglutamatergic neurons of the ventral tegmental area establish local synaptic contacts with dopaminergic and nondopaminergic neurons. *J Neurosci*. 2010 Jan 6;30(1):218-29.

This research will be presented by Marisela Morales during the NIDA Mini-Convention: Frontiers in Addiction Research in a session titled "A Fresh Look at Dopamine Release and Uptake." The Session (#5) will take place at the San Diego Marriott Hotel on Friday, Nov. 12, from 2:15 – 4:15 p.m.

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Adolescent rats may be more severely affected by prolonged nicotine exposure

Drug addiction is a developmental disease, often beginning during adolescence. Because adolescent brains are undergoing extensive developmental changes, they may be uniquely sensitive to the effects of addictive drugs, like nicotine, making them more vulnerable to addiction. A recent animal study funded by NIDA has identified some specific short and long-term gene changes in the brain's reward system that may contribute to increased vulnerability of adolescents to nicotine addiction. Researchers performed whole genome microarray analysis (GMA)—examining an animal's entire genetic profile—on adolescent and adult male rats exposed to chronic nicotine (or saline) for two weeks to look for age-specific changes in gene expression in the VTA, a brain region linked to the rewarding effects of most drugs of abuse. GMA was either performed immediately following chronic nicotine exposure, or after animals were allowed to undergo 30 days of withdrawal. Researchers found that rats displayed striking age-dependent differences in gene expression patterns following chronic nicotine exposure. Compared to adults,

adolescent rats had twice as many genes in the VTA that were persistently changed (i.e., changed immediately in response to chronic nicotine and remained changed over time) and five times as many genes showing delayed regulation (i.e., no change immediately after nicotine exposure, but significant changes following withdrawal). These results suggest that the adolescent brain may be significantly more sensitive to the effects of chronic nicotine at the transcriptional level even after nicotine use stops, and that these effects may not only persist well into adulthood and but may also augment responses to later drug exposure.

Doura MB, Luu TV, Lee NH, Perry DC. Persistent gene expression changes in ventral tegmental area of adolescent but not adult rats in response to chronic nicotine. *Neuroscience*. 2010 Jul 13.

For more information on persistent gene expression, please refer to the NIDA Mini-Convention: Frontiers in Addiction Research conference agenda and note Session 3, "Using Model Organisms to Discover Unanticipated Pathways to Addiction." This session will take place at the San Diego Marriott Hotel on Friday, Nov. 12, from 10:30 a.m. – 12:15 p.m.

Individual impulsivity linked to natural variations in the dopamine system

SPeople vary widely in their decision-making processes. Impulsivity plays a particularly important role in the internal deliberation process and thus in defining an individual's decision-making style. Dopamine (DA) has been thought to play a key role in impulsivity, yet researchers have not identified the precise mechanisms that link dopamine signaling to differences in impulsivity. In this study, NIDA researchers investigated how people's individual differences in DA activity related to differences in impulsive traits. Researchers used a brain scanning approach to visualize the brains of 32 healthy human volunteers and correlated changes in DA receptor activity (specifically the D2/D3 receptor subtypes) in the midbrain with amphetamine-induced DA release in the striatum and scores on the Barratt Impulsiveness Scale. They found that higher levels of impulsivity were predictably associated with lower DA D2/D3 receptor binding and increased amphetamine-induced DA release suggesting that an impaired DA system could underlie a deficit in impulse control, which is one of the behavioral hallmarks

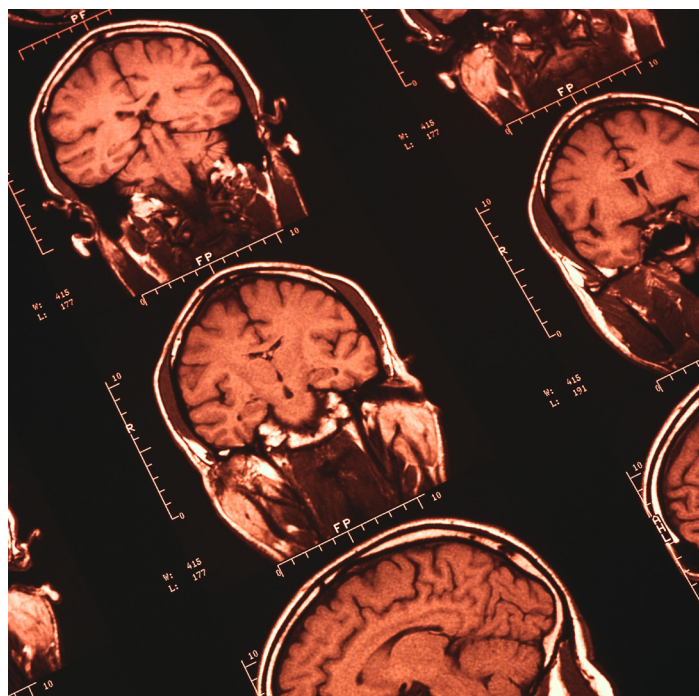
of substance abuse. These findings shed critical new light on the biological underpinnings of individual differences in impulsivity.

Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Shelby ES, Smith CE, Kessler RM, Zald DH. Dopaminergic network differences in human impulsivity. *Science*. 2010 Jul;329(5991):532.

For more information on dopaminergic system differences, please refer to the NIDA Mini-Convention: Frontiers in Addiction Research conference agenda and note Session 5, "A Fresh Look at Dopamine Release and Uptake." This session will take place at the San Diego Marriott Hotel on Friday, Nov. 12, from 2:15 – 4:15 p.m.

Brain regions involved in regulating craving

Drug craving is one of the hallmarks of addiction. Therefore, learning to control craving is a key component of behavioral therapies to treat it. Not much is known, however, about the neural systems that control craving. This study used functional magnetic resonance imaging (fMRI) to measure brain activity in twenty-one adult daily cigarette smokers. Participants underwent fMRI



scans while viewing cigarette and food-related images. During each viewing session, participants were instructed to either think about the immediate feelings and consequences of consuming the pictured item (i.e., NOW), which has been shown to induce robust craving, or the long-term consequences of repeatedly consuming the pictured substance (i.e., LATER), a strategy for controlling craving, and then rate how much they craved the item seen in the trial. Researchers showed that when study participants actively tried to curb or 'down-regulate' their cravings using the LATER strategy, they showed increases in brain activity in areas associated with regulating emotion and cognition (such as the prefrontal cortex), and decreased activity in areas of the brain known to be highly sensitive to cues associated with drug use (such as the ventral striatum). These changes in brain activity further correlated

increased risky behavior in adolescence could be explained partly by increased motivation to obtain positive outcomes

with self-reported craving scores. These results give insight into the mechanisms that enable cognitive strategies to effectively regulate craving, suggesting that the neural dynamics are similar to those involved in regulating other emotions. As such, the study "provides a methodological tool and conceptual foundation for studying [the] ability [to control craving] across substance using populations and developing more effective treatments for substance use disorders," note the authors.

Kober H, Mende-Siedlecki P, Kross EF, Weber J, Mischel W, Hart CL, Ochsner KN. Prefrontal-striatal pathway underlies cognitive regulation of craving. *Proc Natl Acad Sci USA* 2010; 107(33): 14811-6.

For more information on prefrontal-striatal pathway, please refer to the NIDA Mini-Convention: Frontiers in Addiction Research conference agenda and note Session 6, "Connectivity of the Human Brain and its Disruption by Drugs of Abuse." This session will take place at the San Diego Marriott Hotel on Friday, Nov. 12, from 4:35 – 6:20 p.m.

Increased prediction error signals in adolescents linked to increased reward seeking

Adolescence is a unique developmental period often distinguished by risky choices and actions as compared with children and adults. Although previous research shows that teens may be hypersensitive to rewards, the aspect of reward processing responsible for this is unknown. Researchers funded by NIDA used functional magnetic resonance imaging (fMRI) to identify which aspects of reward processing might be responsible for teens' enhanced sensitivity to rewarding stimuli. Taking advantage of prior knowledge, the researchers zeroed in on two key functions that contribute to reward seeking, namely the assigning of value to something that demands attention or a specific action and the prediction of error (i.e., the difference between the expected value of an action and the actual outcome). By analyzing fMRI brain scans of teens as they completed computerized learning tasks, researchers identified brain regions whose responses varied when the subject engaged either of those functions (valuation or prediction error) and tested how those responses changed from childhood to adulthood. The results of this study are consistent with the presence of specific developmental differences in prediction error—related to increases in dopamine signaling—such that increased risky behavior in adolescence could be explained partly by increased motivation to obtain positive outcomes (as opposed to decreased sensitivity to potentially negative outcomes). This study provides important new insight for guiding future studies of adolescent development.

Cohen JR, Asarnow RF, Sabb FW, Bilder RM, Bookheimer SY, Knowlton BJ, Poldrack RA. A unique adolescent response to reward prediction errors. *Nat Neurosci*. 2010 Jun;13(6):669-71.

For more information on dopaminergic prediction error, please refer to the NIDA Mini-Convention: Frontiers in Addiction Research conference agenda and note Session 5, "A Fresh Look at Dopamine Release and Uptake." This session will take place at the San Diego Marriott Hotel on Friday, Nov. 12, from 2:15 – 4:15 p.m.

Pre-quit reactivity to smoking-related images may signal higher risk of smoking relapse

Relapse is common among people trying to quit smoking. Knowing if a person is at high risk of relapse could help tailor treatments more effectively. In a recent study funded by NIDA, researchers used functional magnetic imaging (fMRI) to determine if patterns of brain activity in response to smoking-related images before a quit attempt were predictive of smoking relapse. Before quitting, research participants underwent fMRI while viewing smoking-related (or neutral) images as well as Emotional Stroop (ES) testing to assess their emotional responses to seeing smoking-related words. All participants quit for at least 24 hours during an 8-week cessation phase (with access to weekly individual behavioral intervention, nicotine patch, gum, or lozenge as needed). Following 24-hours of abstinence, participants were divided into two groups based on whether they smoked (i.e., slip group) or didn't (i.e., abstinence group) during the cessation phase. Those who eventually slipped during their quit attempt showed increased pre-quit brain reactivity in brain regions implicated in emotion, motor planning and motor execution and decreased functional connectivity between brain regions involved in cognitive control and the integration of emotional responses. These findings may be useful in identifying individuals at highest risk, even before a quit attempt, which could facilitate more personalized treatment, improved tobacco-dependence treatment outcomes, and reduced smoking-related morbidity and mortality.

Janes AC, Pizzagalli DA, Richardt S, Frederick BD, Chuzi S, Pachas G, Culhane MA, Holmes AJ, Fava M, Evins AE, Kaufman MJ. Brain Reactivity to Smoking Cues Prior to Smoking Cessation Predicts Ability to Maintain Tobacco Abstinence. *Biological Psychiatry*. 2010 17(6): 365-373.

For more information on brain reactivity to smoking, please refer to the NIDA Mini-Convention: Frontiers in Addiction Research conference agenda and note Session 6, "Connectivity of the Human Brain and its Disruption by Drugs of Abuse." This session will take place at the San Diego Marriott Hotel on Friday, Nov. 12, from 4:35 – 6:20 p.m.

Novel epigenetic mechanism in the brain helps explain cocaine's addictiveness

Chronic use of drugs, such as cocaine, can cause long-lasting changes in the patterns of gene expression in the brain, which may contribute to addiction. These changes are called epigenetic because they influence genetic traits without changing a gene's DNA sequence. NIDA researchers recently identified an important mediator of cocaine's

results from this study are the first to show that cocaine acts, at least in part, to alter reward pathways in the brain

epigenetic effects in the nucleus accumbens—a key area of the brain's reward pathway. Researchers gave several doses of cocaine to young mice to assess the epigenetic impact of chronic cocaine administration relative to a single dose. Only animals exposed to chronic cocaine developed a strong preference for cocaine as adults. In addition, these animals showed a significant reduction in the expression of G9a, an enzyme that demethylates histones, essentially loosening up the packaging of genes along the DNA molecule, and thus increasing the likelihood that particular genes will be expressed. Authors were also able to show that by artificially producing large amounts of G9a in the nucleus accumbens, they were able to compensate for cocaine's effects and prevent the establishment of cocaine preference, effectively inhibiting the animal's 'craving' for cocaine. Results from this study offer new critical information about the molecular processes underlying addiction and is the first to show that cocaine acts, at least in part, to alter reward pathways in the brain by repressing G9a, a demethylating enzyme that regulates histone function and plays a critical role in the control of gene expression. These results establish a crucial role for histone methylation in the long-term actions of cocaine and give us a better understanding

of how repeated cocaine use can modify global patterns of gene expression. “Gaining a better understanding of the genes being regulated through such mechanisms will improve our knowledge of the complex biological basis of drug addiction,” say the authors.

Maze I, Covington HE 3rd, Dietz DM, LaPlant Q, Renthal W, Russo SJ, Mechanic M, Mouzon E, Neve RL, Haggarty SJ, Ren Y, Sampath SC, Hurd YL, Greengard P, Tarakhovsky A, Schaefer A, Nestler EJ. Essential Role of the Histone Methyltransferase G9a in Cocaine-induced Plasticity. *Science*. 2010 Jan 8;327(5962):213-6.

For more information on methyl transferase, please refer to the NIDA Mini-Convention: Frontiers in Addiction Research conference agenda and note Session 3, “Using Model Organisms to Discover Unanticipated Pathways to Addiction.” This session will take place at the San Diego Marriott Hotel on Friday, Nov. 12, from 10:30 a.m. – 12:15 p.m.

A striatal microRNA protects rats against compulsive cocaine-seeking

Cocaine addiction typically involves a gradual loss of control over its use, but our understanding of the molecular mechanisms that regulate the transition from controlled to uncontrolled use is far from complete. This study looked at the mechanisms underlying cocaine consumption by comparing two groups of rats: one with extended daily access and the other with no access. Researchers then analyzed the ventral striatum—a region of the brain found to be critically involved in the processing of drug-related information—and discovered a cocaine-responsive noncoding RNA (called microRNA-212) whose expression is increased in the brains of rats with extended access to cocaine. Rats exhibited a growing dislike for cocaine as levels of microRNA-212 increased, suggesting that microRNA-212 operates to decrease motivation to seek cocaine. The researchers also found that microRNA-212 controls cocaine intake by amplifying the activity of CREB, a known negative regulator of cocaine reward. These findings point to microRNA-212 as a putative protective factor against the development of compulsive drug-seeking behavior that may play a pivotal role in determining vulnerability to addiction. This discovery allows for “an entirely new direction for the development of anti-addiction therapeutics based on the modulation of noncoding RNAs,” note the authors.

Hollander JA, Im HI, Amelio AL, Kocerha J, Bali P, Lu Q, Willoughby D, Wahlestedt C, Conkright MD, Kenny PJ. Striatal microRNA controls cocaine intake through CREB signaling. *Nature*. 2010 Jul 8;466(7303):197-202.

Dopamine receptor expression dynamically changes in the rat nucleus accumbens during cocaine withdrawal

Relapse, even after prolonged periods of abstinence, is a defining feature of addiction and is often triggered by intense cravings. While it is well known that dopamine (DA) receptors in the nucleus accumbens (NA)—a key brain region associated with reward—are critical in mediating relapse to cocaine use, the mechanisms regulating this process remain unclear. In this study, researchers studied DA receptor distribution in the NA of rats taught to self-administer cocaine (or saline) after either the first day of withdrawal, when rats are known to exhibit low levels of cue-induced drug seeking, or withdrawal day 45, when rats are known to exhibit high levels of cue-induced drug seeking. Cocaine exposure induced time- (day 1 or day 45) and region-dependent (i.e., NA shell or core) changes in the expression of three types of DA receptors. There were increases in D1 receptor expression in the NA shell immediately following withdrawal, but normalizing by day 45; decreases in D2 receptor expression in both the NA shell and core, with the shell showing decreases on days 1 and 45 but the core only showing decreases on day 45; and D3 receptor expression increases in the core, but only at 45 days after withdrawal. Although the functional implications of these changes are complex, these data suggest that decreased D2 receptor and increased D3 receptor surface expression in the NA core—among other changes in the NA—may contribute to enhanced cravings and cocaine-seeking behavior after prolonged abstinence.

Conrad KL, Ford K, Marinelli M, Wolf ME. Dopamine receptor expression and distribution dynamically change in the rat nucleus accumbens after withdrawal from cocaine self-administration. *Neuroscience*. 2010 Jun 25.

For more information on dopamine receptors, please refer to the NIDA Mini-Convention: Frontiers in Addiction Research and note Session 5, “A Fresh Look at Dopamine Release and Uptake.” This session will take place at the San Diego Marriott Hotel on Friday, Nov. 12, from 2:15 – 4:15 p.m.

For more information about any item in this *NewsScan*:

- All studies described can be obtained through PubMed (www.pubmed.gov).
- **Reporters**, call the **NIDA Press Office** at 301-443-6245.
- **Congressional staffers**, call **Geoffrey Laredo** at 301-594-6852.

The National Institute on Drug Abuse is a component of the National Institutes of Health, U.S. Department of Health and Human Services. NIDA supports most of the world's research on the health aspects of drug abuse and addiction. The Institute carries out a large variety of programs to inform policy and improve practice. Fact sheets on the health effects of drugs of abuse and information on NIDA research and other activities can be found on the NIDA home page at www.drugabuse.gov. To order publications in English or Spanish, call NIDA's new DrugPubs research dissemination center at 1-877-NIDA-NIH or 240-645-0228 (TDD) or fax or email requests to 240-645-0227 or drugpubs@nida.nih.gov. Online ordering is available at <http://drugpubs.drugabuse.gov>. NIDA's new media guide can be found at <http://drugabuse.gov/mediaguide>.

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